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ANALYSIS OF THE QT INTERVAL IN CLINICAL TRIALS

ALEX DMITRIENKO, PHD, AND BRIAN P. SMITH, PHD
Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, Indiana

We explore adaptive (data-driven) approaches in the analysis of clinical QT data in order to find scientifically-sound solutions for correcting the QT interval for heart rate and for analysis of extreme QT measurements. We demonstrate that predefined QT correction formulas (eg, Bazett and Fridericia formulas) are unreliable when the investigational drug induces heart rate changes. Further, simple data-driven approaches (eg, QT correction formulas derived from baseline data in clinical trials) lead to a substantial inflation of the false positive rate. We discuss a QT interval analysis framework based on repeated-measures models that account for correlation among serial ECG measurements collected on the same subject and drug-induced heart rate changes. We also assess the performance of reference ranges for QT interval currently used in clinical trials.

Key Words: ECG; Cardiac repolarization; QT interval; QT correction for heart rate; Reference ranges

INTRODUCTION

CLINICAL RESEARCHERS WIDELY use the QT interval as an important surrogate endpoint related to cardiac repolarization abnormalities. Drugs inducing QT interval prolongation are known to have the potential to cause polymorphic ventricular tachycardia (Torsades de Pointes) linked to sudden cardiac death (1,2). Several drugs (terfenadine, sertindole, cisapride) were recently removed from the market due to their potential to cause malignant arrhythmias and sudden death. This has intensified regulatory concerns with regard to drug-induced cardiac repolarization and QT interval data have become part of standard safety packages across the pharmaceutical industry.

The analysis of QT interval data collected in clinical trials is complicated by a number of factors. The length of the QT interval is influenced by psychological parameters, such as heart rate, age, gender, circadian rhythm, congenital conditions, and electrolyte disturbances (2). The heart rate is the most influential of these factors. The QT interval is negatively correlated with heart rate, that is, it shortens when heart rate is increased and vice versa. Analyses of raw QT measurements are often misleading because they do not account for heart rate variability. To be able to interpret drug-induced changes in the QT interval, one needs to correct the QT interval for heart rate in order to remove the correlation.

The most common way of correcting the QT interval is to standardize it to a convenient reference value, for example, a heart rate of 60 bpm. Many QT correction formulas have been proposed in the ECG literature, for example, Malik (3) lists 20 correction formulas. The most frequently cited QT correction formula was created by Bazett (4). This correction formula is defined as

Reprint address: Alex Dmitrienko, Eli Lilly and Company, Lilly Corporate Center, Drop Code 2233, Indianapolis, IN 46285. E-mail: dmitrienko_alex@lilly.com.

$QTc = QT/RR^{1/2}$, where QTc denotes the corrected QT interval and RR denotes the length of the RR interval (RR interval equals 60 divided by heart rate). The Fridericia QT correction formula (defined as $QTc = QT/RR^{1/3}$) is also widely used in medical research and clinical trials (5).

The two popular formulas are hardly universal and fail to account for substantial variability observed across different clinical studies. They are known to perform poorly in the presence of drug-induced heart rate changes. Fenichel and Koerner (6) state that "drugs that increase the heart rate pose a special problem, since an apparent QTc difference between drug and placebo might in fact be an artifact of increased heart rate and imperfect correction for rate." The performance of the Bazett and Fridericia formulas as well as current approaches to the problem of QT interval correction for heart rate will be discussed in the next section.

It is also important to recognize the effect of the circadian rhythm or the timing of ECG recording on the QT interval. The circadian rhythm is known to introduce a large amount of spontaneous variability that is likely to mask or amplify drug-induced changes in the QT interval depending on when the ECG recording is obtained (7,8). One way to deal with this issue is to study within-subject QT changes. For example, dynamic analysis of QT data using Holter monitoring is described by Lande et al. (9). Malik (3) demonstrates the advantages of repetitive ECG analyses in a small study with 32 subjects. However, this solution is hardly practical in most Phase II and III trials. Only a few ECG measurements per patient are typically taken in the majority of large clinical trials and thus, the ECG data are too sparse to model individual QT-RR relationships. It is customary to minimize spontaneous QT variability in clinical trials by requiring that ECG recordings be obtained at the same time of the day.

An accurate analysis of QT measurements collected in clinical trials requires the development and adoption of guidelines for interpretation and statistical analysis of the QT interval. Despite the importance of this surrogate endpoint, there is currently no consensus regarding the proper analysis of the QT interval in clinical trials. Several recent ECG publications emphasize the lack of a scientifically-sound methodological framework addressing issues such as correction of the QT interval for heart rate, analysis of QT data in the presence of heart rate changes, reference ranges for QTc interval, and so forth (3,10). A report of the European Society of Cardiology (11) published in 2000 points out that "recommendations and guidelines for the preclinical and clinical screening and assessment of any new drug with regard to its potential electrophysiological effects are urgently needed."

Recently published regulatory guidance documents provide a basis for developing guidelines for the analysis of the QT interval in clinical trials. The Committee for Proprietary Medicinal Products (CPMP) points to consider document (12) published in December 1997 discusses analysis and presentation of QT data including the analysis of mean changes and extreme observations. This document, however, focuses only on the Bazett QT correction method whose accuracy has been questioned in the ECG literature. The draft Health Canada guidance document (13) released in March 2001 is partially based on the CPMP points to consider document and deals with similar QT analysis issues. The Food and Drug Administration (FDA) has not published formal guidelines for evaluating the effect of new drugs on cardiac repolarization. A white paper (6), prepared by two FDA medical officers, stresses the need for preclinical assessments to help identify drugs that have a potential to alter ventricular repolarization but issues related to the statistical analysis of QT data are dealt with only briefly.

This paper is concerned with the development of a framework for the analysis of QT data with an emphasis on data-driven QT analysis methodologies. In the next section we will discuss the issues related to heart rate corrections and analysis of mean changes in the QT interval. We will quantitatively assess the performance of predefined QT correction formulas (eg, Bazett method), and trial-

specific and model-based QT corrections. It will be shown that the model-based method is the most effective QT analysis method that works for drugs inducing heart rate changes. The third section deals with the analysis of individual QTc measurements and reference ranges for the QTc interval. We will discuss ways to help standardize definitions of clinically abnormal QT measurements.

QT INTERVAL CORRECTION FOR HEART RATE

As stated in the first section, the duration of the QT interval is strongly correlated with heart rate. To accurately interpret findings related to the QT interval, clinical researchers need to address this correlation in their analyses of the QT interval. This can be accomplished by using QT correction formulas published in the literature or derived from available ECG data.

The two widely used QT correction formulas (the Bazett and Fridericia formulas) were computed over 80 years ago from small samples of subjects. Their adequacy has been questioned both in clinical (3,14–17) and preclinical publications (10). We assessed the performance of the Bazett and Fridericia formulas by computing the Pearson correlation coefficient between the corrected QT interval and RR interval from 10056 drug-free ECG measurements. These measurements were collected in 36 clinical trials sponsored by Eli Lilly and Company (the database will be referred to as the Lilly ECG database). The results are presented in Table 1.

A QT correction formula is expected to eliminate the QT-RR correlation, in which case the Pearson correlation coefficient will be close to zero. However, as seen in Table 1, both the Bazett-corrected and Fridericia-corrected QT intervals are still strongly correlated with the RR interval. Spence et al. (10) and Vandenhende (18) reported similar results in beagle dog studies. This correlation with the RR interval adversely affects performance of the Bazett and Fridericia corrections. The use of these QT correction formulas (or any other empirical QT corrections) in drug development raises the same concerns as the use of historical controls and is likely to introduce substantial bias in the analysis of QT interval. Malik (3) emphasizes that "no reliable conclusions can be based on the application of previously published heart rate correction formulas in studies of drug-induced QT interval prolongation."

Data-driven QT corrections are becoming increasingly popular in clinical trials. Instead of using a predefined formula such as Bazett's, a QT correction formula is developed from drug-free ECG data collected in one or several studies. Data-driven formulas of this type better reflect the nature of the QT-RR relationship in each particular patient population. Once the formula has been derived, it is used to analyze the entire set of QT and RR data (ie, collected at baseline, on therapy, and during follow-up). To illustrate this concept, we fitted a linear regression model to the drug-free QT and RR data in the Lilly ECG database. According to the regression model, the mean QT equaled 228 + 184 RR ms. This regression model generated a linear QT correction formula of the form $QTc = QT + 184(1 - RR)$. The QTc interval obtained from this formula is no longer correlated with the RR interval because the derived formula provides a perfect fit to the QT

TABLE 1
Correlation Between the Corrected QT Interval and the RR Interval

The Corrected QT Interval	Pearson Correlation Coefficient
Bazett-corrected QT interval	−0.324
Fridericia-corrected QT interval	0.280

Note: Both correlation coefficients are significantly different from 0 at a two-sided 0.001 level.

and RR data in the Lilly ECG database. This QT correction formula can be used to correct QT measurements for heart rate across all clinical trials in the database. A similar methodology was recently utilized in intramuscular ziprasidone trials (19). A nonlinear QT correction formula ($QTc = QT/RR^{0.4}$) was based on the QT-RR relationship observed in ECG data obtained at baseline from patients in the combined oral and intramuscular ziprasidone databases.

QT correction formulas derived from large ECG databases are better than previously published QT corrections. However, they may prove unreliable if the baseline QT-RR relationship varies across studies included in the database. In this case, it is customary to generate a trial-specific QT correction formula from the trial's baseline ECG data. Spence et al. (10) advocate the use of study-specific baseline-generated QT corrections in moderate to large studies and indicate that a correction derived from data pooled across related studies may be preferable in smaller trials.

It is also critical to ensure that the statistical analysis of the QT interval is performed properly. QT interval data are typically analyzed by computing a QTc interval using a predefined or baseline-generated correction and then comparing the QTc changes across the treatment groups using simple ANOVA models. A review of the Lilly ECG database indicates that ECG parameters (including QT and RR intervals) collected from the same subject are highly correlated, even though they may have been taken weeks apart. This correlation is typically referred to as longitudinal correlation. Naïve analyses of the QTc interval based on simple ANOVA models suffer from an inflated false positive rate because they do not account for drug-induced heart rate changes and longitudinal correlation. To alleviate the outlined deficiency of QTc analyses commonly performed in clinical trials, one can employ regression models for longitudinal data. These models are commonly used in the analysis of measurements collected in a repeated fashion, for example, efficacy endpoints collected on the same patient at different times. Dmitrienko and Smith (unpublished data; 2000) developed a framework for the analysis of the QT interval based on repeated-measures models of this type. The proposed repeated-measures model includes the RR interval as a covariate and accommodates the longitudinal correlation among serial ECG measurements. The model-based approach eliminates the bias introduced by traditional QT correction methods and increases the power of detecting drug-related QT interval prolongation. This analysis can be performed using most commercially available statistical software packages, for example, SAS, S-plus, and BMDP.

In what follows, we will describe a numerical simulation that was conducted to assess the performance of several QT correction methods in a hypothetical clinical trial. The assumptions used in this simulation are based on real QT and RR data collected in Eli Lilly trials and the results reflect trends seen in real clinic trials. The QT and RR data were assumed to be collected at baseline and endpoint in a two-arm clinical trial (experimental drug versus placebo) with 200 patients in each treatment group. The QT and RR data were analyzed using the Bazett and Fridericia corrections, a correction formula derived from the baseline data (baseline-generated correction), and a model-based approach proposed by Dmitrienko and Smith (unpublished data; 2000). The QT-RR data were simulated using the following procedure.

Placebo Group

The heart rate was normally distributed with mean 60 bpm and standard deviation 15 bpm both at baseline and endpoint. At each fixed RR value, the QT interval was also normally distributed with mean 228 + 184 RR ms and standard deviation 18 ms both at baseline and endpoint. The Pearson correlation coefficient between baseline and endpoint RR values for the same subject was 0.8. Similarly, the Pearson correlation coefficient between baseline and endpoint QT values was 0.8.

Experimental Group

The heart rate at baseline followed a normal distribution with the same parameters as in

the placebo group. However, the mean heart rate at endpoint was higher. Specifically, it was assumed that the mean heart rate at endpoint was 60, 65, and 70 bpm with a standard deviation of 15 bpm. Further, the QT interval was assumed to decrease with increasing heart rate so that the overall relationship between QT and RR remained the same. Specifically, at each fixed RR value, the QT data were normally distributed with a mean of 228 + 184 RR ms and a standard deviation of 18 ms both at baseline and endpoint. The Pearson correlation coefficients between baseline and endpoint RR and QT values for the same subject equaled 0.8.

The assumptions are also summarized graphically in Figures 1 and 2. It is shown in Figures 1 and 2 that the numerical simulation was set up in such a way that no changes in either heart rate or QT-RR relationship were observed in the placebo group and the experimental drug was assumed to increase the heart rate. It is important to emphasize that even though the experimental drug increased the heart rate, the QT-RR relationship was exactly the same in the two arms at both baseline and endpoint. In other words, the experimental drug induced heart rate changes but did not delay cardiac repolarization. Therefore, if the QT interval is properly corrected for heart rate, one should not expect to see any difference between the two treatment groups in corrected QT changes.

The QT-RR data were generated 5000 times. The mean QT changes and false positive rates were computed for the four QT analysis methods. The effect of the experimental drug on the QT interval was assessed by comparing the mean changes from baseline to endpoint in the corrected QT interval between the

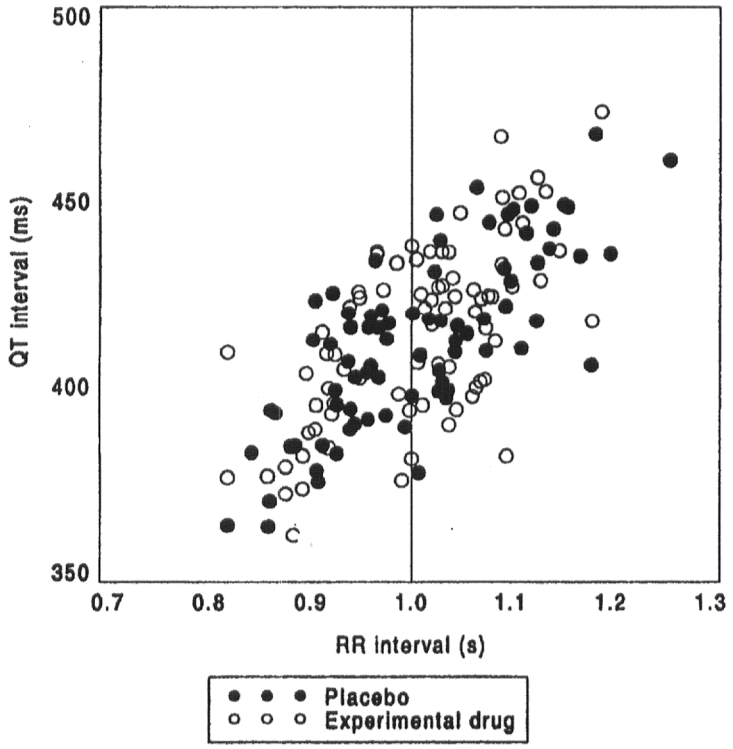

FIGURE 1. Plot of simulated QT and RR data at baseline.

Note: The vertical line is drawn at the mean RR interval. The mean RR interval is equal to 1 s in both treatment groups, ie, the mean heart rate is 60 bpm.

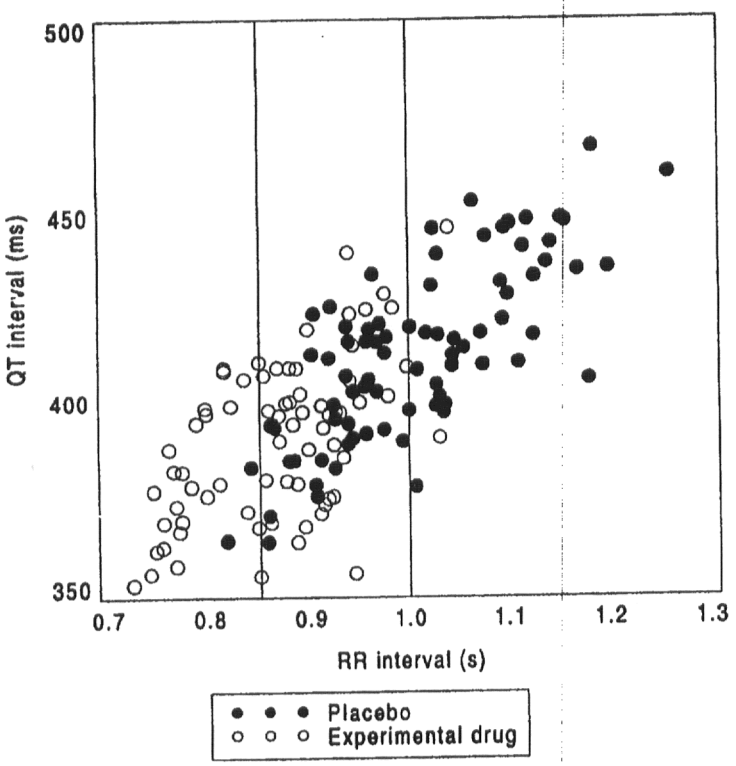

FIGURE 2. Plot of simulated QT and RR data at endpoint.

Note: The vertical lines are drawn at the mean RR interval in the two treatment groups. The mean RR interval is equal to 1 s in the placebo group and 0.85 s in the experimental group, ie, the experimental drug increased heart rate by 10 bpm. Note that the QT-RR patterns in the two treatment groups are the same at baseline and endpoint. This means that the experimental drug does not alter cardiac repolarization.

two treatment groups. The p-value for Bazett, Fridericia, and baseline-generated corrections was computed using a two-sample t-test. The p-value for the model-based QT analysis method was calculated using a repeated-measures model with an adjustment for longitudinal correlation among serial ECG measurements and drug-induced heart rate change. All analyses were performed at a two-sided significance level of 0.05 and thus, the false positive rates are expected to be close to 5%. Table 2 presents the results of the numerical simulation.

Table 2 demonstrates intrinsic limitations of the Bazett and Fridericia QT correction formulas. Utilizing the Bazett correction results in a significant QT interval prolongation in the experimental group compared to placebo when the experimental drug increases the heart rate. This QT prolongation is purely artificial. The Fridericia correction formula undercorrects QT interval and introduces a negative bias. The baseline-generated QT correction formula does not bias the mean change in the corrected QT interval. However, it inflates the false positive rate with the magnitude of inflation proportional to the mean heart rate change in the experimental group. This is caused by the fact that this correction is based on baseline QT and RR data only. As a result, it fails to account for longitudinal correlation among serial ECG measurements and heart rate changes from baseline to endpoint. Only the model-based QT analysis method produces unbiased estimates of the drug effect on cardiac repolarization and preserves the false positive rate.

TABLE 2
Mean Differences and False Positive Rates in Corrected QT Interval Change by QT Analysis Method

QT Analysis Method	Mean Increase from Baseline to Endpoint in Heart Rate in the Experimental Group		
	No Increase	5 bpm Increase	10 bpm Increase
Bazett			
Mean difference (ms)	–0.03	2.52	5.78
False positive rate (%)	4.9	33.1	92.8
Fridericia			
Mean difference (ms)	–0.04	–3.41	–5.84
False positive rate (%)	4.8	54.7	94.0
Baseline-generated			
Mean difference (ms)	–0.03	–0.08	–0.09
False positive rate (%)	5.1	7.1	13.8
Model-based			
Mean difference (ms)	–0.03	–0.08	–0.09
False positive rate (%)	4.7	4.2	4.3

Note: The mean difference in corrected QT change is defined as the mean corrected QT change in the experimental drug group minus the mean corrected QT change in the placebo group. A positive mean difference indicates that the experimental drug prolongs the QT interval compared to placebo.

These simulation results are representative of outcomes observed in real clinical trials sponsored by Eli Lilly and Company.

It is worth noting that the model-based approach can be extended to account for subject-specific changes in the QT-RR relationship. QT analysis methods currently used in most clinical trials are "sample-based." This means they assume that the QT-RR relationship is constant across the sample of interest. Malik (3) and Molnar et al. (20) show that the QT-RR patterns vary considerably from one individual to another and propose to explicitly model this variability by using individual subject-specific QT correction formulas. This "subject-based" approach is clearly superior to "sample-based" analyses. Clinical researchers are encouraged to employ individualized QT correction formulas in studies with multiple ECG recordings per subject.

REFERENCE RANGES FOR QT INTERVAL

It is often stated in the clinical trial literature that the analysis of abnormal measurements in safety data (commonly referred to as outlier analysis) assumes greater importance than the analysis of mean changes over time (21). Many ECG publications emphasize the importance of studying extreme QT observations and present reference intervals for the QT interval (12,13,22,23). Reference ranges are available for several QT correction methods, for example, the Hodges correction formula in (23). However, most of the publications deal with the Bazett QT correction.

The CPMP points to consider document (12) presents gender-specific reference ranges for the Bazett-corrected QT interval. According to the CPMP criteria, adult males and females are considered to have a prolonged QT interval if their Bazett-corrected QT interval is longer than 450 and 470 ms, respectively. These reference ranges were derived in Moss and Robinson (22) from a sample of 578 healthy subjects. They are fairly close to the traditional definition of QT prolongation based on the 440 ms threshold (22).

The CPMP criteria are widely used across the pharmaceutical industry. For example, we found that the CPMP criteria were used in

all recent FDA submissions including intramuscular ziprasidone (19), oral ziprasidone (24), and telithromycin (25). These criteria were recently adopted in the draft Health Canada guidance document (13). The CPMP criteria are based on the Bazett QT correction method and consequently suffer from the problems outlined in the second section. The Bazett-corrected QT interval is strongly correlated with heart rate, which causes the reference ranges to change with increasing heart rate. This fact considerably complicates the interpretation of outlier analyses based on the CPMP criteria. Further, the CPMP criteria do not account for age-related changes in QT interval.

MacFarlane and Lawie (23) show that the 96% range for the Bazett-corrected QT interval increases markedly with age in the Glasgow study (1338 subjects). For example, the 96% range is 386 to 477 ms in females in the 18- to 29-age group and 392 to 506 ms in females older than 50 years. De Bruyne et al. (26) also report that the prevalence of Bazett-corrected QT intervals longer than 440 ms increased with age in the Rotterdam study (5566 subjects). To illustrate the limitations of the CPMP criteria, we computed the percentage of patients in the Lilly ECG database whose QT interval is classified as prolonged according to the CPMP criteria. Table 3 summarizes the results in patients with low and high heart rates by age.

Table 3 clearly indicates that the percentage of patients with prolonged QT interval increases dramatically with increasing heart rate and age. Specifically, older patients with increased heart rates (≥80 bpm and ≥40 years) are 63 times more likely to be classified as having a prolonged QT interval than younger patients with bradycardia (<80 bpm and <40 years). As a result, an investigational drug that increases heart rate but does not alter cardiac repolarization is likely to markedly increase the incidence of extensive QT prolongation according to the CPMP criteria.

It is also very common to perform an outlier analysis based on the 500 ms threshold (19,24). A subject is classified as having a prolonged QT interval if the length of his or her corrected QT interval exceeds 500 ms. The use of this criterion was justified by Makkar et al. (2). Based on the analysis of English-language publications between 1980 and 1992, Makkar et al. (2) showed that the Bazett-corrected QT interval was longer than 500 ms in 89.5% of reported cases of Torsades de Pointes. However, this 500 ms criterion ignores the strong correlation between the duration of QT interval and age. As a result, the criterion will also overestimate the prevalence of prolonged QT measurements among older patients in clinical trials.

The use of data-driven methodologies should alleviate the outlined deficiency of the CPMP reference ranges and 500 ms criterion. Accurate data-driven reference ranges can be calculated from the baseline QT and RR data in any large clinical trial. Reference ranges derived from a large database of drug-free ECG data are preferable in smaller trials, for example, Phase I trials and most Phase II trials. Corrected QT measurements typically follow a normal or nearly normal distribu-

TABLE 3
Percentage of Patients with Prolonged Bazett-corrected QT Interval According to the CPMP Criteria

Heart Rate (bpm)	Age (years)	Number of Patients	Percentage of Patients with Prolonged QT Interval (%)
<60	18–39	604	0.17
	≥40	861	1.74
≥80	18–39	614	5.37
	≥40	1179	10.69

tion. Reference ranges for the corrected QT interval can be derived using standard parametric or nonparametric statistical methods by excluding the top 1% or 2.5% of the observations. These methods are similar to those employed in setting up reference ranges for clinical laboratory data. Examples of a successful application of the nonparametric approach to construct reference ranges for QT interval can be found in MacFarlane and Lawie (24). One can also derive tolerance limits advocated by Chuang-Stein and Nickens (21,27). It is important to compute age- and gender-specific reference ranges to account for the effect of these prognostic factors on cardiac repolarization. This can be accomplished using the same statistical methods, however, a large sample size is required to arrive at accurate reference ranges across all of the subsets of interest.

CONCLUSIONS

A review of clinical publications, regulatory documents, and FDA submission packages indicates that the issue of identifying drug-induced QT prolongation has become one of FDA's top priorities. The discussion in these publications and documents revolves primarily around issues related to QT correction for heart rate and analysis of extreme QT measurements. On one hand, a plethora of correction methods have been proposed in the literature and the number of publications on this topic continues to increase. On the other hand, at this moment there appears to be no scientific or regulatory agreement on the general principles of the analysis of QT data collected in clinical trials.

Clinical trial sponsors are often encouraged to analyze the QT interval using several correction formulas and then required to explain the observed discrepancies (see, for example, the draft Health Canada guidance document [13]). Malik (3) points out that one is virtually guaranteed to see discrepancies among the results obtained by an application of QT correction formulas found in the ECG literature. We came to the same conclusion when assessing the performance of the Bazett and Fridericia formulas in the second section (see Table 2). The observed discrepancies simply indicate that the performance of predefined QT correction methods is unsatisfactory. Most widely used QT corrections have been computed from small samples and thus, are inherently unreliable. Furthermore, the QT-RR relationship may not be reproducible across studies and patient populations. Recent studies clearly demonstrate that the QT-RR relationship is likely to be different in every individual (3,20).

Data-driven QT analysis methods are gradually replacing the much criticized Bazett formula. However, drug developers need to exercise caution when using study-specific correction formulas derived from baseline (drug-free) QT and RR data. We showed in the second section that naïve data-driven analyses of the QT interval are prone to a substantial false positive rate inflation when the experimental drug increases or decreases the heart rate. The QT analysis framework outlined by Dmitrienko and Smith (unpublished data; 2000) is superior to predefined QT correction formulas as well as baseline-generated correction formulas. This framework is based on repeated-measures models widely used in the analysis of longitudinal data in clinical trials. The model-based QT analysis method explicitly accounts for important data features such as drug-induced heart rate changes and longitudinal correlation among ECG measurements collected on the same subject. It also allows one to adjust QT analyses for factors known to influence the duration of QT interval, for example, age, gender, and serum electrolyte imbalances. This QT analysis method provides drug developers with an accurate tool for separating drug-related QT prolongation from spontaneous variability and accurately identifying drugs with a potential to provoke potentially fatal arrhythmias. Vandenhende (18) successfully applied a similar approach based on a repeated-measures model for QT and RR data in the derivation of reference ranges for the QT interval in beagle dogs.

Outlier analyses of QT measurements are performed in clinical trials to help identify

individual patients with delayed repolarization. These analyses are based on abnormality criteria similar to those employed in the analysis of safety laboratory data (20). It is critical to ensure that these criteria reflect specific clinical trial patient populations and account for important prognostic factors. The normal limits for QT interval proposed in the CPMP points to consider document (12) do not account for age-related changes in the length of the QT interval. As a result, analyses of extreme QT measurements using the CPMP criteria are prone to errors. The performance of outlier analyses can be substantially improved if drug developers employ study-specific reference ranges for the QT interval or reference ranges calculated from data pooled across studies conducted in the same patient population.

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